EXHIBITS 1-2

REDACTED IN THEIR ENTIRETY

EXHIBIT 3

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OPPOSITION

TO

EP3018211B

Nippon Shinyaku Co., Ltd.

AND

National Center of Neurology and Psychiatry

BY:

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Contents

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EXTENT OF OPPOSITION

EP3018211B (hereinafter '**211**) is opposed in its entirety for all designated states.

REQUESTS

We request that '211 be revoked in its entirety.

If anything other than complete revocation is envisaged, we request Oral Proceedings. This request is ongoing and applies in respect of any matter on which we have not been heard.

THE PATENT

'211 was filed as EP15199455.5, a divisional of EP11821996.3, which was filed as PCT/JP2011/70318 on 31 August 2011 and published as WO2012/029986 on 8 March 2012.

It claims priority from Japanese patent application JP2010196032 ("P1") filed on 1 September 2010.

However, as will be detailed below, the claimed subject-matter of '211 extends **beyond** the content of both the divisional application as filed and the parent application as filed. **Therefore, the claimed subject-matter is entitled only to the date the amendments were filed, namely 10 November 2016**.

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DOCUMENTS CITED

D1 – EP2612917A

D2 – Oxford Dictionary of Biochemistry and Molecular Biology, Oxford University Press, revised edition, 2000

D3 – WO 2010/048586

D4 – US 2010/0168212

D5 – L.J. Popplewell et al., *Neuromuscular Disorders*, **2010**, 20(2), 102-110

D6 – WO 2014/153240

D7 - US 6784291

D8 - US 2010/0130591

D9 - WO 2004/083432

D10 – A. Aartsma-Rus et al., "Functional Analysis of 114 Exon-Internal AONs for Targeted DMD Exon Skipping: Indication for Steric Hindrance of SR Protein Binding Sites," Oligonucleotides (2005) 15(4): 284-297

D11 - WO 2006/000057

D12 - US 2007/0082861

D13 - WO 2011/057350

D1 is the English translation of the parent PCT application as published in accordance with Article 153(4) EPC. Although D1 published on 10 July 2013, the relevant publication date is that of the WO publication, namely 8 March 2012.

D2 is cited as evidence of the normal meaning of the word "complementary" in molecular biology and biochemistry.

D13 was published under the PCT on 19 May 2011, before the PCT filing date of the opposed patent. For the reasons explained in detail herein, as the opposed patent is not entitled to claim priority from P1 – thereby meaning that D13 forms prior art to the opposed patent under Article 54(2) EPC.

All of the other documents were published before the priority date P1 – thereby meaning that they all form prior art to the opposed patent under Article 54(2) EPC irrespective of whether the claim to priority is valid.

CLAIMED SUBJECT-MATTER OF THE OPPOSED PATENT

The granted claim set is reproduced in full in Annex 1.

There is only one independent claim, claim 1, which recites as follows:

1. *An antisense oligomer which causes skipping of the 53rd exon in the human dystrophin gene,* ***consisting of*** *a nucleotide sequence* ***complementary to the 36th to the 60th nucleotides*** *from the 5' end of the 53rd exon in the human dystrophin gene.*

In this regard, the Opposition Division's attention is drawn to the following features of the claim.

Base sequence

Firstly, the term *"consisting of"* takes its usual closed meaning – in other words, that the sequence of the oligomer has the recited bases **and no others**.

The claim therefore limits the nucleotide sequence to a nucleotide sequence **complementary to the 36th to the 60th nucleotides** of exon 53. It can therefore be understood to have 25 bases.

The normal meaning of the term *"complementary"* in molecular biology and biochemistry in relation to an oligonucleotide chain is that the base sequence of the oligonucleotide chain is a complementary base sequence to the sequence of the target polynucleotide chain.

D2 confirms that the term "complementary base sequence" means *"a sequence in a polynucleotide in which* ***all*** *the bases are able to form base pairs with a sequence of bases in another polynucleotide chain"*.

The DNA base sequence of exon 53 of the human dystrophin gene is disclosed as SEQ ID NO: 1 in '211. The 36th to 60th nucleotides thereof (read from 3' to 5' as this is the target sequence) have the base sequence CAACGGAGGCCAAGACTTCCACAAG.

This means that, under Watson-Crick base pairing rules (A pairing to T or U, and G to C), the normal meaning of the base sequence of the oligonucleotide chain **complementary** to it would be **GTTGCCTCCGGTTCTGAAGGTGTTC** or **GUUGCCUCCGGUUCUGAAGGUGUUC**.

However, paragraph [0026] of the granted specification indicates that the term "complementary" is intended by the patentee to have a **broader** meaning, as follows:

"As used herein, the term "complementary nucleotide sequence" is not limited only to nucleotide sequences that form Watson-Crick pairs with target nucleotide sequences, but is intended to also include nucleotide sequences which form Wobble base pairs. As used herein, the term Watson-Crick pair refers to a pair of nucleobases in which hydrogen bonds are formed between adenine-thymine, adenine-uracil or guanine-cytosine, and the term Wobble base pair refers to a pair of nucleobases in which hydrogen bonds are formed between guanine-uracil, inosine-uracil, inosine-adenine or inosine-cytosine. As used herein, the term "complementary nucleotide sequence" does ***not only*** *refers to a nucleotide sequence* ***100% complementary to the target*** *nucleotide sequence but also refers to a complementary nucleotide sequence that* ***may contain, for example, 1 to 3, 1 or 2, or one nucleotide non-complementary to the target nucleotide sequence****."*

This paragraph of the description therefore **does not restrict** the number of **non-complementary** bases.

In view of this, claim 1 of '211 should be interpreted such that the **base sequence** of the antisense oligomer may either be a 100% complementary to the target sequence, or may differ by **an unknown number** of non-complementary bases.

Antisense chemistry

Claim 1 of '211 only recites the nature of the base sequence. In contrast, it does **not** limit in any way the **chemistry** of the **backbone** of the antisense oligomer. Consequently, it covers **all** known antisense chemistries, including but not limited to the following:

- natural (RNA/DNA) oligomers having ribose or deoxyribose base-bearing subunits bonded together by phosphate intersubunit linkages;
- morpholino oligomers having morpholine base-bearing subunits, in particular phosphorodiamidate morpholino oligomers (PMOs) wherein the morpholine base-bearing subunits are bonded together by phosphorodiamidate intersubunit linkages
    - Evidence that the claims cover morpholino, in particular PMO, oligomers can be found at paragraphs [0056] (which indicates they are *"the oligomer of the present invention"*) to [0109]
- 2'O-methylphosphorothioate (2'-OMePS) oligomers having 2'O-methylribose base-bearing subunits bonded together by phosphorothioate intersubunit linkages.
    - Evidence that the claims cover (2'-OMePS) oligomers can be found at paragraph [0054] (which indicates they are *"the oligomer of the present invention"*)
- Peptide nucleic acids having amino acid base-bearing subunits bonded together by amide (peptide) bonds.
    - Evidence that the patentee intends the term to cover (2'-OMePS) oligomers can be found at paragraphs [0110] (which indicates they are *"the oligomer of the present invention"*) to [0111]

Both of the above issues, of course, mean the claims are essentially **unlimited** both in the nucleotide sequence and the antisense chemistry.

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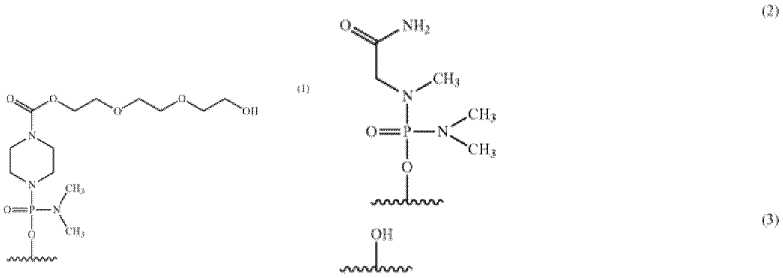
No definition of group at 5' end

It is noted that, in the description, '211 recites several groups which may be present at the 5' end of the molecule. Specifically, the following groups (1) to (3) are referred to in the detailed description (see, for example, the top of page 4 of '211):



However, the **claims** of '211 do **not** include any such limitation, and consequently cover antisense oligomers having **any** group at the 5' end of the oligomer.

The lack of any meaningful limitation in the claims (when interpreted in the light of the patentee's own definitions in the description) has consequences as regards added matter, sufficiency and inventive step as indicated below. In particular, the lack of a definition of the group at the 5'-end has consequences for inventive step in view of the data presented in '211, as explained in more detail below.

ADDED SUBJECT-MATTER – ARTICLES 123(2) & 76(1) EPC

Claim 1 extends beyond content of divisional and parent applications as filed

For the reasons outlined below, at least claim 1 of '211 constitutes **an unallowable intermediate generalisation** between the broadest disclosure and the Examples and therefore extends beyond both the content of the divisional application EP15199455.5 as filed, contrary to Article 123(2) EPC, and that of the parent application EP11821996.3 as filed, contrary to Article 76(1) EPC.

The description and drawings of the divisional application as filed are identical to those of the English translation of the parent PCT application as filed on EPO regional phase entry (with the exception that the claims of the parent as filed on EPO regional phase entry are reproduced as "items" at the end of the description of the divisional). In view of this, for ease of reference, both will be referred to generally in this Opposition as "the application as filed" unless there is a need to draw a distinction between the two.

It is established Boards of Appeal case law, and long established practice before the EPO, that intermediate generalisations violate Article 123(2) EPC. See Case Law of the Boards of Appeal (9th Edition, English version, II.E.1.9), pages 482 and 483, which summarises the key case law which prohibits intermediate generalisations under Article 123(2) EPC:

*"According to established case law (as summarised e.g., in **T 219/09** or **T 1944/10**), it will normally not be allowable to base an amended claim on the extraction of isolated features from a set of features originally disclosed only in combination, e.g. a specific embodiment in the description (**T 1067/97**, **T 714/00**, **T 25/03, T2095/12**).*

*Amended subject-matter that amounts to a generalisation of a particular embodiment disclosed in the original application but is still more specific than the original definition of the invention in general terms is often called an "intermediate generalisation" (see e.g. **T 461/05**, **T 191/04**; see also **T 2311/10**) and sometimes an "intermediate restriction" (see **T 461/05**, **T 879/09**, **T 2537/10**), Other decisions understand "intermediate generalisation" to refer to **an undisclosed – and thus unallowable** - **combination of selected features lying somewhere between an originally broad***

disclosure and a more limited specific disclosure *(**T 1408/04**). An intermediate generalisation is different from a simple generalisation (as e.g. in **T 910/03**, **T 461/05**), since in the former case a definition of the invention in general terms forms part of the original disclosure (**T 461/05**)."*

In the case of divisional applications, the same principles are to be applied for determining whether subject-matter extends beyond the content of the earlier application as filed (**G 1/05**, OJ 2008, 271, point 5.1 of the Reasons – as cited in Case Law of the Boards of Appeal (9th Edition, English version, II.E.1.1), page 433. Therefore, all objections relating to contraventions of Article 123(2) EPC as regards the divisional as filed are equally applicable as contraventions of Article 76(1) EPC as regards the parent as filed.

As indicated above, Claim 1 of '211 reads as follows:

*"An antisense oligomer which causes skipping of the 53rd exon in the human dystrophin gene, consisting of a nucleotide sequence complementary to **the 36th to the 60th nucleotides** from the 5' end of the 53rd exon in the human dystrophin gene."*

As noted above, this claim specifies the target sequences, but **not** the antisense chemistry.

It is acknowledged that the general paragraphs in the description which relate to the "disclosure of the invention", and specifically page 3, line 32 to page 4 line 10 (embodiment [1]) and page 7 line 31 to page 8, disclose in a generalised manner "oligomers of the present invention" consisting of antisense oligomers consisting of a nucleotide sequence complementary to the following nucleotides of exon 53:

31st to 53rd	32nd to 53rd	33rd to 53rd	34th to 53rd	35th to 53rd	36th to 53rd
31st to 54th	32nd to 54th	33rd to 54th	34th to 54th	35th to 54th	36th to 54th
31st to 55th	32nd to 55th	33rd to 55th	34th to 55th	35th to 55th	36th to 55th
31st to 56th	32nd to 56th	33rd to 56th	34th to 56th	35th to 56th	36th to 56th
31st to 57th	32nd to 57th	33rd to 57th	34th to 57th	35th to 57th	36th to 57th
31st to 58th	32nd to 58th	33rd to 58th	34th to 58th	35th to 58th	36th to 58th

No fewer than 36 target sequences within exon 53 ranging from the regions of 31st to the 55th to the 36th to the 58th nucleotides of exon 53 are disclosed in these general paragraphs. Antisense oligomers consisting of nucleotide sequences complementary to **these target sequences** can be considered disclosed in a generalised manner (i.e. **without** limitation of the antisense chemistry) in the application as filed.

In total contrast, there is **no** such **generalised** disclosure **anywhere** in the application as filed for an antisense oligomer consisting of a nucleotide sequence complementary to **the 36th to the 60th nucleotides** of exon 53. **None** of the general paragraphs in the application as filed disclose an antisense oligomer (of any antisense chemistry) consisting of a nucleotide sequence complementary to this target sequence.

The **sole basis** in the application as filed for an antisense oligomer targeting the 36th to 60th nucleotides of exon 53 is in **Test Example 6** – namely in Table 7 at page 53, in which an oligomer designated "H53_36-60" is disclosed as SEQ ID NO: 57 on page 54. It is **admitted** by the patentee, both in the basis table provided with the divisional application as filed on 11 December 2015 and in the response dated 10 November 2016, that this is the sole basis for claim 1.

However, in contrast to the sequences disclosed more generally in embodiment [1], the application as filed does **not** disclose either this oligomer or any of the other oligomers in Table 7 **in a generalised manner**. In contrast, page 53 lines 16 and 17, which describe the oligomers in Table 7, disclose that **all** of the antisense oligomers of Table 7 **are "2'-O-methoxy-phosphorothioates (2'-OMe-S-RNA)**." (This term can be understood to read "2'-O-**methyl**-phosphorothioates").

This of course means that **all** of the Examples disclosed in Table 7 constitute a **combination of features**: a nucleotide sequence as disclosed therein **and** a 2'-O-methylphosphorothioate chemical backbone.

In contrast, as indicated above, claim 1 as currently on file is **completely silent** on the antisense chemistry, and therefore covers an antisense oligomer having **any** chemical backbone.

As is immediately apparent from the above, an amendment which introduces **only** the feature of the base sequence of SEQ ID NO: 57, but **not** the antisense chemistry with which it is disclosed **in combination**, constitutes **an intermediate generalisation** which violates Article 123(2) EPC. For the same reasons, it also extends beyond the content of the parent application as filed and violates Article 76(1) EPC.

As the patentee is of course aware, this objection has previously been raised in third party observations while the application was pending. However, the Examining Division **erred** in departing from its initial view (as indicated in the Communication dated 9 November 2018) that the above amendment violated Article 123(2) EPC and allowing the application to proceed to grant, for the following additional reasons.

The patentee's response dated 11 March 2019 cites an additional passage from Case Law of the Boards of Appeal, II.E.1.7 (corresponding to II.E.1.9 of the 9th Edition) relating to intermediate generalisations. In this regard, the Opponent has the following comments.

In T714/00 (Reasons 3.3) the Board reasoned as follows:

"Extracting an isolated feature from an originally disclosed combination and using it for delimiting claimed subject-matter can only be allowable under the concept of Article 123(2) EPC if that feature is ***not inextricably linked*** *with* ***further features of that combination****."*

As the Opposition Division will understand from the above, an antisense molecule does not simply comprise a base sequence – the skilled person must consider **the whole molecule**, **including** the chemical backbone.

The patentee also relies heavily on T962/98 in its response dated 11 March 2019. The catchword of T962/98, which the patentee quotes, reads as follows:

"There may exist situations where some characteristics taken from a working example may be combined with other features disclosed in a more general context without necessarily creating an objectionable intermediate generalization. However, under Article 123(2) EPC, such an intermediate generalization is only admissible if the skilled person can recognize ***without any doubt*** *from the application as filed that*

those characteristics are not closely related to the other characteristics of the working example and apply directly and unambiguously to the more general context. In other terms, in order to be acceptable, this intermediate generalization must be the result of unambiguous information that a skilled person would draw from the review of the example and the content of the application as filed (cf. point 2.5)."

The patentee also refers to the summary of the experimental results of Test Example 6 as disclosed at page 57, lines 21-25 (as corrected) and alleges that this provides generalised teaching for an antisense oligomer that targets within the region from position 31-61 from the 5' end of exon 53.

We disagree. As indicated above, Test Example 6 of the application as filed discloses the antisense molecules of Table 7, **all** having a 2'-O-Me PS chemical backbone. The results described therein are therefore **specific** to **those molecules** and **cannot** be used to provide basis for a more generalised feature which is nowhere disclosed in the application as filed.

Put simply, and as stated above, Test Example 6 and Table 7 of the application as filed do **not** provide **generalised** teachings of AONs. In contrast to the AONs described above, which the patentee **defined** as *"oligomers of the present invention"*, nucleotide sequences complementary to **the 36th to the 60th nucleotides** of exon 53 are **not** part of that invention. The sole disclosure of such a compound targeting the 36th to the 60th nucleotides of exon 53 is in Test Example 6 and Table 7, where a single compound having the sequence: GUUGCCUCCGGUUCUGAAGGUGUUC, as defined in SEQ ID NO:57 **and** 2'OMePS chemistry is disclosed.

In addition, the patentee alleges that aim of the invention should be considered more generally as identification of the target regions within exon 53, and that the particular antisense chemistry is not singled out as being crucial. However, while this statement may be considered reasonable in respect of the antisense compounds referred to above disclosed more generally in embodiment [1] of the application as filed, it does not change the fact that the sole disclosure of an antisense oligomer targeting the 36th to 60th nucleotides of exon 53 is in Table 7 which specifically recites 2'-O-Me PS antisense oligomers.

In this regard, the specification repeatedly and specifically defines the **invention** using the defined term *"oligomers of the present invention"* as AONs consisting of sequences complementary to the 36 specified target sequences.

However, the AONs of Test Example 6 and Table 7 are not described as *"oligomers of the present invention."* Rather, the compounds of this example are simply described as *"antisense oligomers of 2'-O-methoxy-phosphorothioates."*

Nowhere in Test Example 6 and Table 7 does the patentee use the term *"oligomers of the present invention"*. It is **only** with respect to the *"oligomers of the present invention"* (i.e. AONs complementary to the 36 target sequences) that the chemical backbones are disclosed in a generalised manner.

The patentee specifically and intentionally limited that which they considered their invention to the *"oligomers of the present invention"* consisting of a nucleotide sequence that is complementary to the 36 target sequences. The AON "H53_36-60" in Test Example 6 and Table 7 does not fall within that invention, and therefore claiming it in a generalised manner violates Article 123(2) EPC.

Finally, the correction of the translation error on page 57 of the translated application as referred to in the response dated 11 March 2019 (namely, *"exons 31-61"* to *"positions 31-61"*) is **completely irrelevant** to the issue that Test Example 6 and Table 7 do not provide a generalised disclosure of AONs targeting the 36th to 60th nucleotides of exon 53. It does not change the fact that Test Example 6 only discloses H53_36-60 with the sequence of SEQ ID NO: 57 and 2'-OMe-PS chemistry.

Summarising, for all of the reasons indicated above, Claim 1 of '221 represents an unallowable intermediate generalisation having no basis in the application as filed, and therefore contravenes Article 123(2) and 76(1) EPC.

At least by their dependency on claim 1, claims 2-4 also contravene Article 123(2) and 76(1) EPC.

LACK OF PRIORITY – ARTICLE 87 EPC

Subject-matter of claim 1 is not disclosed in P1

It is noted that no English translation of P1 is currently on file before the EPO. However, an inspection of the original Japanese of P1 clearly indicates that Test Example 6 and Table 7 of '211, which the Patentee admits is sole basis for the subject-matter of claim 1, is not disclosed anywhere in P1.

Therefore, **none** of the specific antisense compounds listed in Table 7, in particular, the specific 2'OMe-PS antisense compound having SEQ ID NO: 57, are disclosed anywhere in D1.

Therefore, Claim 1 of '211, and all claims dependent thereon, cannot validly claim priority from P1. Even if the Opposition Division disagrees with the additional arguments set out below regarding the date to which the claimed subject-matter is entitled, '211 is still only entitled to its PCT filing date of 31 August 2011.

Filing date to which the application is entitled is more than a year after P1

As detailed above, the claimed subject-matter is entitled only to the date the amendments were filed, namely 10 November 2016.

This is, of course, more than a year after the filing date of P1, namely 1 September 2010.

Therefore, for this additional reason, Claim 1 of '211, and all claims dependent thereon, cannot validly claim priority from P1.

NOVELTY – ARTICLE 54 EPC

Lack of novelty in view of D1

As detailed above, the claimed subject-matter of '211 is entitled only to the date the amendments were filed, namely 10 November 2016.

D1 was published before this filing date.

D1 discloses (as SEQ ID NO: 57) the sequence H53_36-60, which is an antisense oligomer, consisting of a nucleotide sequence complementary to the 36th to the 60th nucleotides from the 5' end of the 53rd exon in the human dystrophin gene, having a 2'-O-Me PS chemical backbone.

This causes skipping of the 53rd exon in the human dystrophin gene – see Test Example 7 and in particular the results shown in Figures 16 and 17 for H53_36-60.

Therefore, claim 1 lacks novelty in view of D1.

The features of claims 2-4 of '211 are also disclosed in D1, as follows:

- Claim 2 – embodiment [2] – page 3 line 27
- Claim 3 – embodiment [3] – page 3 lines 28-29
- Claim 4 – embodiment [4] – page 3 lines 30-32

Therefore, all claims of '211 lack novelty in view of D1.

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Lack of novelty in view of D6

For the same reasons as detailed above, in view of the date to which the claimed subject-matter is entitled, D6 is also citable for novelty against '211.

D6 discloses (as SEQ ID NO: 1) the sequence H53A(36+60) – see D6, page 65, Example 2. This is an antisense oligomer, consisting of a nucleotide sequence complementary to the 36th to the 60th nucleotides from the 5' end of the 53rd exon in the human dystrophin gene, having a phosphorodiamidate morpholino (PMO) chemical backbone.

This AON causes skipping of the 53rd exon in the human dystrophin gene – see D7, page 70, Example 7 and in particular the results shown in Figures 3 and 4 for oligomer H53A(+36+60).

Therefore, claim 1 of '211 lacks novelty in view of D6.

INVENTIVE STEP – ARTICLE 56 EPC

In the unlikely event that the independent claims are deemed novel, the claims additionally lack inventive step for the reasons cited below.

Lack of inventive step over D5

D5 can be considered the closest prior art for the determination of inventive step. D5 discloses a number of PMOs targeting exon 53 of which at least 12 target regions that overlap with that of the instant claims. We further note that D8-D13 also disclose a number of AONs that target exon 53. For example, D8-D13 disclose at least 29 AONs that target regions within exon 53 that overlap the claim AONs. Accordingly, the claims lack an inventive step over D8-D13 as well.

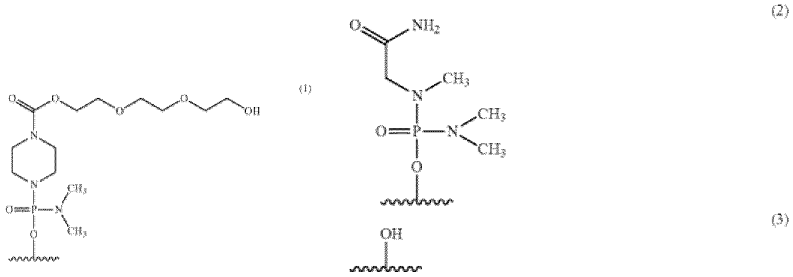
D5 was cited (as D1) by the Examining Division during prosecution. However, the Examining Division **erred** in departing from its initial opinion (as expressed in the Search Opinion dated 16 March 2016 and its subsequent Communications dated 9 February 2017 and 8 September 2017), for at least the reasons outlined below.

In its response dated 16 March 2018, the patentee provided comparative data between the oligomer "H53_36-60" as against "H53_33-62" (which is stated to be the antisense compound H53A30/1 of D3). Specifically, Patentee provided a description of the tested oligomers consisting of:

> **H53_36-60:** 5′- GTTGCCTCCGGTTCTGAAGGTGTTC -3′; corresponding to SEQ ID NO: 57 of the present application, and complementary to the 36th to the 60th nucleotides from the 5′ end of the human dystrophin gene's 53rd exon; and
> **H53_33-62:** 5′- CTGTTGCCTCCGGTTCTGAAGGTGTTCTTG-3′; corresponding to H53A30/2 of D1, and complementary to the 33rd to the 62nd nucleotides from the 5′- end of the human dystrophin gene's 53rd exon.
> **H53_36-56:** 5′- CCTCCGGTTCTGAAGGTGTTC -3′; corresponding to SEQ ID NO: 35 of the present application, and complementary to the 36th to the 56th nucleotides from the 5′ end of the human dystrophin gene's 53rd exon; and

Importantly, Patentee does not indicate many of the chemical features of the tested oligomers. Critically, Patentee fails to specify what functional group is present at the 5' end of the tested oligomers. Paragraph [0112], of '211 provides that *"[i]n an*

oligomer of the present invention, the 5' end may be any of chemical structures (1) to (3) below, and preferably is (3)-OH".



We note that such groups were known and desirable in the prior art. For example, D7 states at column 7, lines 13-30:

"The solubility of the antisense compound, and the ability of the compound to resist precipitation on storage in solution, can be further enhanced by derivatizing the oligomer with a solubilizing moiety, such as a hydrophilic oligomer, or a charged moiety, such as a charged amino acid or organic acid. The moiety may be any biocompatible hydrophilic or charged moiety that can be coupled to the antisense compound and that does not interfere with compound binding to the target sequence. The moiety can be chemically attached to the antisense compound, e.g., at its 5' end, by well-known derivatization methods. One preferred moiety is a defined length oligo ethylene glycol moiety, such as ***triethylene glycol****, coupled covalently to the 5' end of the antisense compound through a* ***carbonate linkage, via a piperazine linking group forming a carbamate linkage with triethylene glycol****, where the second piperazine nitrogen is coupled to the 5'-end phosphorodiamidate linkage of the antisense."*

Here, D7 describes the moiety of Group (1) of the instant disclosure.

The description further provides (Test Example 7 – see '211 pages 34 and 35) that oligomers of the present invention having 5' end Group (3) (PMOs 8 and 14 – see Table 2) were superior to oligomers of the present invention having the same nucleotide sequence but having 5' end Group (1) (PMOs 3 and 13). (See Figure 19.)

The inventors concluded (see paragraph [0204] and Figure 19) that *"[t]hese results showed that the sequences with —OH group at the 5' end provide a higher skipping efficiency even in the same sequences."*

In contrast, nowhere do the Experimental Results submitted with the response of 16 March 2018 describe what the group at the 5' end of any of the tested oligomers are or even if there is a group at the 5' end that corresponds to those disclosed in the patent.

In fact, an examination of Figure 19 shows that PMOs having a Group (3) -OH at the 5' end (PMOs 8 and 3) showed about a 1.375-2.2 fold increase in exon skipping activity as compared PMOs having the same nucleobase sequence and a Group (1) moiety at the 5' end (PMOs 14 and 13). For example, at 10µmol dose, exon 53 skipping for the PMO No. 8 with a Group (3) -OH was approximately 65% whereas exon 53 skipping for PMO 14 having a Group (1) moiety was approximately 30%; a 2.17-fold difference. Similarly, exon 53 skipping for PMO 3 having a Group (3) -OH was about 62% whereas exon 53 skipping for PMO 13 having a Group (1) moiety was about 30%; a 2.07-fold difference.

In their response dated 16 March 2018, Patentee indicated that the exon 53 skipping of "H53_36-60" was "1.5-fold higher than that of H53_33-62…."However, at least because Patentee did not indicate which group was at the 5' end of "H53_36-60," "H53_36-56," or "H53_33-62," one cannot determine whether any differences in exon skipping is a result of the nucleobase sequence of the tested compounds **or** the 5' group of the tested compounds, whether it is one of Groups (1), (2), or (3) or another moiety.

Therefore, it is impossible to conclude that the effects described in the Experimental Results provided by the patentee in its response dated 16 March 2018 would be applicable to a corresponding antisense molecule having the same base sequence and **any** of the described 5' end groups. The comparative data do **not** therefore provide sufficient evidence that a technical effect is **associated with the difference from the closest antisense molecule** as disclosed in D5.

In the absence of any evidence of such a technical effect, the objective problem can only be formulated as providing an **alternative** to the antisense molecules of D5.

For the reasons previously stated in the Communications, this is entirely obvious over D5. Therefore, the subject-matter of Claim 1 and all claims dependent thereon lacks inventive step over D5.

Lack of inventive step across entire scope of claims

The patent purports to solve the problem of providing further compounds which induce exon 53 skipping.

However, even if the Opposition Division were to decide that **some** subject-matter in the patent solves this technical problem, this still leaves a vast amount of subject-matter falling within the claims as not solving any technical problem, for the reasons set out below.

For example, as indicated above the patent claims at least provide **no limitation** on the chemistry of the backbone – as evidenced by the multiplicity of antisense chemistries referred to above which the patentee's own definition in the patent recites as *"the invention"* – nor any limitation on the group at the 5' end of the oligomer.

As remarked above, this of course means the claims are **practically unlimited** with respect to the antisense chemistry.

There is, of course, no evidence in the patent that any technical problem is solved across this unlimited scope.

This of course means that there is no evidence in the patent that an inventive step is exhibited **across the entire breadth of the claims**, as required by T939/92 and subsequent case law.

Hence, for this additional reason, claim 1 lacks inventive step.

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DEPENDENT CLAIMS LACK INVENTIVE STEP

The remaining claims additionally lack novelty and/or inventive step, for the reasons outlined below:

Claim 2 is dependent on claim 1 and adds the feature that the antisense oligomer is an oligonucleotide.

This feature does not add anything novel or inventive as antisense oligonucleotides are disclosed in the documents filed herewith, for example in D5.

Claim 3 is dependent on claim 2 and adds the feature that the sugar moiety and/or the phosphate-binding region of at least one nucleotide constituting the oligonucleotide is modified.

This feature does not add anything novel or inventive as such modified oligonucleotides are disclosed in the documents filed herewith, for example in D5 which discloses AONs having PMO chemistry.

Claim 4 is dependent on claim 3 and adds the feature that the sugar moiety of at least one nucleotide constituting the oligonucleotide is a ribose in which the 2'-OH group is replaced by any one selected from the group consisting of: OR, R, R'OR, SH, SR, NH_2, NHR, NR_2, N_3, CN, F, Cl, Br, and I, wherein R is an alkyl or an aryl and R' is an alkylene.

This feature does not add anything novel or inventive as 2'OMe-PS oligonucleotides are disclosed in the documents filed herewith.

INSUFFICIENCY – ARTICLE 83 EPC

For a number of reasons as set out below, the patent is insufficiently disclosed in a number of fundamental respects. For these reasons at least, the entire patent therefore lacks sufficient disclosure, contrary to Article 83 EPC.

Lack of sufficient disclosure across entire scope of claims

Even if the Opposition Division were to consider that some subject-matter falling within the independent claims is sufficiently disclosed (which we refute), the claims still lack sufficient disclosure across their entire breadth, for the reasons set out below.

For example, as indicated above the patent claims at least provide **no limitation** on the chemistry of the backbone – as evidenced by the multiplicity of antisense chemistries referred to above which the patentee's own definition in the patent recites as *"the invention"* – nor any limitation on the group at the 5' end of the oligomer.

As remarked above, this of course means the claims are **practically unlimited** with respect to the antisense chemistry.

There is, of course, no evidence in the patent that antisense oligomers can be prepared, and would effective in exon 53 skipping, across this unlimited scope. This of course means that there is no enabling disclosure **across the entire breadth of the claims**, as required by T409/91 and subsequent case law.

Hence, for this additional reason, all claims contravene Article 83 EPC.

CONCLUSION

None of the claims as granted meets the requirements of the EPC.

Therefore the patent should be revoked in its entirety.

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ANNEX 1 – GRANTED CLAIMS

1. An antisense oligomer which causes skipping of the 53rd exon in the human dystrophin gene, consisting of a nucleotide sequence complementary to the 36th to the 60th nucleotides from the 5' end of the 53rd exon in the human dystrophin gene.

2. The antisense oligomer according to claim 1, which is an oligonucleotide.

3. The antisense oligomer according to claim 2, wherein the sugar moiety and/or the phosphate-binding region of at least one nucleotide constituting the oligonucleotide is modified.

4. The antisense oligomer according to claim 3, wherein the sugar moiety of at least one nucleotide constituting the oligonucleotide is a ribose in which the 2'-OH group is replaced by any one selected from the group consisting of: OR, R, R'OR, SH, SR, NH_2, NHR, NR_2, N_3, CN, F, Cl, Br, and I, wherein R is an alkyl or an aryl and R' is an alkylene.

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Notice of opposition to a European patent

I. Patent opposed

Patent No.	EP3018211
Application No.	EP15199455.5
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	07 August 2019
Title of the invention	ANTISENSE NUCLEIC ACIDS

II. Proprietor of the patent

first named in the patent specification	Nippon Shinyaku Co., Ltd
Opponent's or representative's reference	X119884EPA GAD

III. Opponent

Name	Sarepta Therapeutics, Inc.
Address:	215 First Street Cambridge MA Massachusetts 02142 United States of America
State of residence or of principal place of business	United States of America
Multiple opponents (see additional sheet)	☐

IV. Authorisation

1. Representative

	D Young & Co LLP
Association No.:	672
Registration No.:	00106720
Address of place of business	120 Holborn London EC1N 2DY United Kingdom
Telephone/Fax	+44 (0) 20 7269 8550 / +44 (0) 20 7269 8555
Additional representative(s) on additional sheet/see authorisation	☐

Authorisation(s)

is/are enclosed ☐

has/have been registered under No. ☐

V. Opposition is filed against

the patent as a whole ☒

claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not patentable (Art. 100(a) EPC) because:

- it is not new (Art. 52(1); Art. 54 EPC) ☒
- it does not involve an inventive step (Art. 52(1); Art. 56 EPC) ☒
- patentability is excluded on other grounds, namely articles ☐

(b) the patent opposed does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 100(b) EPC; see Art. 83 EPC). ☒

(c) the subject-matter of the patent opposed extends beyond the content of the application/of the earlier application as filed (Art. 100(c) EPC, see Art. 123(2) EPC). ☒

VII. Facts (Rule 76(2)(c) EPC)

presented in support of the opposition are submitted herewith on an attached document ☒

VIII. Other requests:

- Oral proceedings are hereby requested auxiliarily.

IX. Evidence presented

D1	Patent document	EP2612917 (A1) , 10.07.2013 original file name: D1 - EP2612917A1.PDF attached as: Published-Evidence-1.PDF
D10	Non-patent literature - article	Aartsma-Rus, Annemieke et al., "Functional Analysis of 114 Exon-Internal AONs for Targeted DMD Exon Skipping: Indication for Steric Hindrance of SR Protein Binding Sites" Oligonucleotides, Vol. 15, 2005 original file name: D10 - Aartsma-Rus et al Oligonucleotides 2005 15(4) 284-297.PDF attached as: Published-Evidence-9.PDF
D11	Patent document	WO2006/000057 (A1) , 05.01.2006 original file name: D11 - WO2006000057A1.PDF attached as: Published-Evidence-10.PDF
D12	Patent document	US2007/0082861 (A1) , 12.04.2007 original file name: D12 - US2007082861A1.PDF attached as: Published-Evidence-11.PDF
D13	Patent document	WO2011/057350 (A1) , 19.05.2011 original file name: D13 - WO2011057350A1.PDF attached as: Published-Evidence-12.PDF
D2	Other evidence	Oxford Dictionary of Biochemistry and Molecular Biology, Oxford University Press, revised edition, 2000 original file name: D2 - Oxford Dictionary of Biochemistry and Molecular Biology.PDF attached as: Other-evidence-1.PDF
D3	Patent document	WO2010/048586 (A1) , 29.04.2010 original file name: D3 - WO2010048586A1.PDF attached as: Published-Evidence-2.PDF
D4	Patent document	US2010/0168212 (A1) , 01.07.2010 original file name: D4 - US2010168212A1.PDF attached as: Published-Evidence-3.PDF
D5	Non-patent literature - article	Popplewell, Linda J. et al., "Comparative analysis of antisense oligonucleotide sequences targeting exon 53 of the human DMD gene: Implications for future clinical trials" Neuromuscular Disorders, Vol. 20, No. 2, 2010 original file name: D5 - L.J. Popplewell et al. Neuromusc Dis 2010.PDF attached as: Published-Evidence-4.PDF
D6	Patent document	WO2014/153240 (A2) , 25.09.2014 original file name: D6 - WO2014153240A2.PDF attached as: Published-Evidence-5.PDF
D7	Patent document	US6,784,291 (B2) , 31.08.2004 original file name: D7 - US6784291B2.PDF attached as: Published-Evidence-6.PDF
D8	Patent document	US2010/0130591 (A1) , 27.05.2010 original file name: D8 - US2010130591A1.PDF attached as: Published-Evidence-7.PDF

D9	Patent document	WO2004/083432 (A1) , 30.09.2004 original file name: D9 - WO2004083432A1.PDF attached as: Published-Evidence-8.PDF

X. Payment

Method of payment: Debit from deposit account

The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated in the fees section below.

Currency: EUR

Deposit account number: 28050042

Account holder: D Young & Co LLP

Refunds

Any refunds should be made to EPO deposit account: 28050042

Account holder: D Young & Co LLP

Fees	Factor applied	Fee schedule	Amount to be paid
010 Opposition fee	1	815.00	815.00
Total:		EUR	815.00

	A Forms	Details:	System file name:
A-1	Form for notice of opposition		ep-oppo.pdf

	B Attached document files	Original file name:	System file name:
B-1	1. Facts and arguments	Opposition Statement.pdf	OPPO.pdf

	C Attached evidence files	Original file name:	System file name:
C-1	1. Patent document	D1 - EP2612917A1.PDF	Published-Evidence-1.PDF
C-2	2. Patent document	D3 - WO2010048586A1.PDF	Published-Evidence-2.PDF
C-3	3. Patent document	D4 - US2010168212A1.PDF	Published-Evidence-3.PDF
C-4	4. Patent document	D6 - WO2014153240A2.PDF	Published-Evidence-5.PDF
C-5	5. Patent document	D7 - US6784291B2.PDF	Published-Evidence-6.PDF
C-6	6. Patent document	D8 - US2010130591A1.PDF	Published-Evidence-7.PDF
C-7	7. Patent document	D9 - WO2004083432A1.PDF	Published-Evidence-8.PDF

C-8	8. Patent document	D11 - WO2006000057A1.PDF	Published-Evidence-10.PDF
C-9	9. Patent document	D12 - US2007082861A1.PDF	Published-Evidence-11.PDF
C-10	10. Patent document	D13 - WO2011057350A1.PDF	Published-Evidence-12.PDF
C-11	1. Non-patent literature - article	D5 - L.J. Popplewell et al. Neuromusc Dis 2010.PDF	Published-Evidence-4.PDF
C-12	2. Non-patent literature - article	D10 - Aartsma-Rus et al Oligonucleotides 2005 15(4) 284-297.PDF	Published-Evidence-9.PDF
C-13	1. Other evidence	D2 - Oxford Dictionary of Biochemistry and Molecular Biology.PDF	Other-evidence-1.PDF

Annotations

Title (Author):

1. Note (for EPO)

Notice of Opposition against EP3018211B (Garreth Duncan)

We file herewith a Notice of Opposition against EP3018211B.

Please find attached our Opposition Statement and cited documents D1 to D13.

Signature of opponent or representative

Place	**Southampton, UK**
Date:	**05 May 2020**
Signed by:	**Garreth Duncan 19318**
Association:	**D Young & Co LLP**
Representative name:	**Garreth Duncan**
Capacity:	**(Representative)**